HSIA
halogenated
solvents
industry
alliance, inc.

March 15, 2017

U.S. Environmental Protection Agency
Docket Center
WJC West Building, Room 3334
1301 Constitution Avenue, NW
Washington, DC 20004

Re: Docket No. EPA-HQ-2016-0737

Dear Sirs:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents producers, distributors, and users of trichloroethylene or TCE. We offer these comments in response to EPA's Risk Evaluation Scoping Efforts under TSCA and specifically as they relate to the circumstances in which trichloroethylene is used, intended to be used, or foreseen to be manufactured, distributed or disposed of in commerce.

HSIA notes at the outset that important uses of TCE are the subject of proposed rules that would largely ban its use in certain applications. 81 Fed. Reg. 91592 (Dec. 16, 2016) (spot cleaning in dry cleaning facilities and aerosol degreasing); 82 Fed. Reg. 7432 (Jan. 19, 2017) (vapor degreasing). The first of these rulemakings failed to comply with the Small Business Regulatory Enforcement Fairness Act as it was not the subject of a Small Business Advisory Review; both are outside the scope of the risk assessment on which they are based in violation of TSCA § 26(l)(4). The deficiencies of the underlying risk assessment have been the subject of a Small Business Advisory Review on June 15, 2016 and EO 12866 meetings at the Office of Management & Budget on September 15 and October 3, 2016, and will be the subject of voluminous comment. **We also urge EPA to take steps now to include a review of these uses as part of the current scoping exercise, so that any future regulation of TCE in spot cleaning in dry cleaning facilities, aerosol degreasing, or vapor degreasing will be based on a risk assessment in compliance with TSCA §§ 6 and 26.**

Overview

Trichloroethylene is a chlorinated solvent that is used extensively in vapor degreasing, metal fabrication, metal cleaning, as a chain transfer agent in the production of polyvinyl chloride, as a feedstock in the manufacture of refrigerants, and to flush out reservoirs and piping for liquid oxygen and liquid hydrogen tanks.

Trichloroethylene is one of the most regulated chemicals in the United States. The Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have established or recommended occupational airborne

exposure limits for trichloroethylene. The OSHA Permissible Exposure Limit (PEL) is an 8-hour weighted average (TWA) of 100 ppm. The ACGIH currently recommends a Threshold Limit Value (TLV) of 10 ppm for an 8-hour Time Weighted Average and 25 ppm for a 15-minute short term exposure limit.

Uses of Trichloroethylene

Vapor Degreasing – Trichloroethylene is used primarily for vapor degreasing, which includes critical cleaning while fabricating, finishing or assembling parts made of zinc, aluminum, brass, bronze, and steel. Industries such as automotive, aerospace and house appliance manufacturers use vapor degreasing to remove soil and metal chips that occur during fabrication.

Adhesives and Coatings – Trichloroethylene is used by the coatings and adhesives industries in the manufacture of adhesives, rubber cements, epoxies, caulks, and adhesive and sealant removers.

Feedstock Use – Trichloroethylene is essential in the manufacture of fluorocarbon refrigerants, most notably HFC-134a. These are used in refrigeration and automotive, household, and industrial air conditioning.

Aerospace Use – Trichloroethylene is used by the aerospace industry to flush out reservoirs and for piping for liquid oxygen and liquid hydrogen tanks.

Metals Cleaning – Trichloroethylene is the primary cleaning solvent for aluminum sheet and strip steel prior to galvanizing. TCE is used because it cleans more thoroughly and several times faster than alkaline cleaners and requires smaller equipment that consumes less energy.

Chemical Processing – Trichloroethylene is critical to the chemical processing industry. It is used in manufacturing photographic and x-ray films, in plastics manufacturing, in ink processing and in agricultural chemicals, among others.

Product Stewardship and Trichloroethylene

Producers and users of trichloroethylene are committed to its continued safe use. Good industrial hygiene practices and the use of personal protective equipment, combined with proper training and environmental, health and safety practices all contribute to safety in the workplace. In the event of an environmental release, containment programs are in place. Many aspects of dealing with a release or spill are now mandated by federal, state and local requirements. Trichloro-ethylene is not sold directly to consumers but may be an ingredient in some consumer products.

Industrial Hygiene

The manufacturers and users of trichloroethylene have a long history of focusing on industrial hygiene as evidenced by extensive personnel monitoring samples collected over many years. One manufacturer has collected more than 50,000 personnel monitoring samples since the late 1970s. With regards to trichloroethylene, that same manufacturer has collected 2,973 samples to

date with 99.87% of the results below the OSHA Permissible Exposure Limit (PEL). In the last 15 years, there has only been a single result above the PEL.

REACH and Trichloroethylene

Under European REACH regulations, manufacturers assess the exposure and risks of substances as part of its registration dossier. One member company reports that its German subsidiary holds an application for authorization under REACH for five uses of trichloroethylene. This application was supported by detailed assessments that demonstrated that the process involving trichloroethylene cannot be replaced by other solutions, the socio-economic benefits of the continued use of TCE, and the exposure and risks related to these uses.

Other Resources

HSIA would like to suggest that EPA consult a very valuable resource with information on the supply, demand, markets and trade of chlorinated solvents. We learned that EPA does have a subscription to this service – IHS Markit. You may want to contact the HIS Markit Director of Specialty Chemical Consulting, Ray Will, at ray.will@ihsmarkit.com, for assistance in using these data.

We appreciate the opportunity to submit these comments and look forward to working with EPA on the path forward in implementing the Lautenberg Act.

Respectfully submitted,

Faye Graul

Faye Graul
Executive Director

BEFORE THE ENVIRONMENTAL PROTECTION AGENCY

Trichloroethylene; Regulation of Certain Uses under TSCA § 6(a)

[EPA-HQ-OPPT-2016-0163; FRL-9949-86]

Comments of the

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March 16, 2017

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The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents producers and users of trichloroethylene (TCE). We offer these comments on EPA's proposed rule banning manufacture of TCE for and use of TCE in aerosol degreasing and in spot cleaning by dry cleaning facilities. 81 Fed. Reg. 91592 (Dec. 16, 2016). This rule, proposed under § 6(a) of the Toxic Substances Control Act (TSCA), is based on a Work Plan Assessment of TCE completed by EPA in June 2014. TSCA was amended in June 2016 by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("Lautenberg Act").

HSIA urges EPA to withdraw the proposed rule, which is based on a very deficient risk assessment.. While EPA is authorized under TSCA § 26(l)(4) to propose a § 6 rule based on a risk assessment completed before TSCA was revised, there is no requirement or deadline for it to do so. The situation is very different for the ten priority compounds designated by EPA under TSCA § 6(b)(2)(A) in December 2016.[1] For these ten designated pollutants, TSCA establishes deadlines for risk assessments and rulemakings. TCE is one of the ten priority compounds, and the better course would be to assess the risks from spot cleaning and aerosol degreasing as part of the required upcoming TCE assessment.

These comments address the following subjects, among others, in detail:

- TSCA § 26(l)(4) requires, for a rule based on a risk assessment completed before TSCA was revised, that the rule must be consistent with "the scope of the completed risk assessment for the chemical substance and consistent with other applicable requirements of § 6." "Although the use of TCE as a solvent degreaser at large commercial/industrial operations" was "not considered in this assessment," EPA nevertheless would prohibit all "commercial use of TCE in aerosol degreasing products," regardless of the size of the facility. This is plainly outside "the scope of the completed risk assessment."

- Further, the TCE Work Plan Assessment does not comply with the requirements of TSCA § 6(b)(4)(F) or TSCA § 26(h) and (i), which are expressly applicable to any EPA "decision based on science" under TSCA § 6. The disparity between the completed risk assessments and the "applicable requirements of § 6" is obvious from even a cursory review of the procedures for risk evaluation under the amended TSCA proposed by EPA earlier this year.

- The Work Plan Assessment expressly relied on hazard values derived directly from a University of Arizona study to estimate non-cancer risk. Several other studies, including two GLP-compliant studies conducted under EPA and OECD guidelines, have been unable to reproduce the effect seen in the Arizona study. The Arizona study has been heavily criticized in the published literature, its results have not been replicated by any other laboratory, and other regulatory authorities (including the California EPA) have rejected the study as deficient.

- Equally, the Work Plan Assessment relies on qualitative and quantitative estimates of cancer risk that are not realistic or justified by any underlying science. EPA estimates a baseline cancer risk from chronic occupational spot cleaning exposures of 1 in 10. Cancer incidence of this magnitude could not go unnoticed, and indeed EPA's estimate is belied by available epidemiology studies of dry cleaning workers which show no such risk. Indeed, two recent large Nordic epidemiological studies, both of which had extensive follow-up of the cohorts, have failed to find an association between TCE and kidney cancer, and these are not addressed in the Work Plan Assessment. Further, EPA's development of a potency factor based on Charbotel *et al.* (2006) directly contravenes the advice EPA received from the National Academy of Sciences.

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[1] 81 Fed. Reg. 91927 (Dec.19, 2016).

- On the exposure side, for spot cleaning EPA relied solely on a 2007 California study, which it recognized may not be representative of US dry cleaning facilities. For aerosol degreasing EPA provided no emissions or monitoring data – thus these are hypothetical exposures. Moreover, the draft TCE assessment, entitled "Degreaser and Arts/Crafts Uses," did not address spot cleaning (except to say that none of those sold to consumers contained TCE), but the final Work Plan Assessment is entitled "Degreasing, *Spot Cleaning* and Arts & Crafts Uses" and includes commercial use of TCE as a spotting agent at dry cleaning facilities.

- Because there was no notice that EPA was addressing spot cleaning, there was no participation by dry cleaner representatives and no peer review of the spot cleaning assessment. Moreover, there was no Small Business Advocacy Review, even though spot cleaning is done by dry cleaners which are virtually all small entities. It is not credible that EPA could certify that the rule would not have a significant economic impact on a substantial number of small entities (SISNOSE), where the dry cleaning industry estimates that 60-90% of retail dry cleaners routinely use TCE on the spotting board (14,130 – 21,195 small businesses) and projects that such a ban will cost 4-5% of gross sales, far more than the 1-3% impact considered SISNOSE.

- Peer review of the draft Work Plan Assessment was scathing. Reliance on the unreproducible Arizona study was harshly criticized. The Chair of the panel noted that it was a screening level assessment, not suitable for use in regulation: "*the Agency acted prematurely in issuing this (screening level)* assessment for public comment. . . . After listening carefully to the comments and contributions from the other members of the Panel, I have concluded that there would *little benefit in revising this draft screening assessment.*"[2] Yet EPA claims the peer review was supportive.

- EPA's determination that TCE use in spot cleaning and aerosol degreasing poses an "unreasonable risk" is based on its assessment of risks to workers. It is clear, however, that TSCA is to be used only when other statutes fail to provide a remedy for unreasonable risks. Worker health and safety fall under the jurisdiction of the Occupational Safety and Health Administration (OSHA), and use of TCE in spot cleaning and spray degreasing is already adequately regulated under the Occupational Safety and Health Act. Congress cannot have meant, in enacting "gap-filling" legislation, to open the door to EPA assuming all authority over the use of hazardous substances in the workplace.

I. Failure of Work Plan Assessment to Comply with TSCA §§ 6, 26

A. Applicable Requirements of TSCA §§ 6, 26

Although the Lautenberg Act made significant changes to TSCA to ensure that EPA would employ the "best available science" in its risk assessments, EPA proposes to rely on a remarkably sketchy and inadequate assessment in its inaugural rulemaking under TSCA § 6. TSCA § 6(b)(4)(F), as revised by the Lautenberg Act, requires that EPA's risk evaluations must, among other things:

- "integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance, including information that is relevant to specific risks of injury to health or the environment and information on potentially exposed or susceptible subpopulations identified as relevant by the Administrator;"

[2] https://www.epa.gov/sites/production/files/2015-09/documents/tce_consolidated_peer_review_comments_september_5_2013.pdf.

- "take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use of the chemical substance;" and

- "describe the weight of the scientific evidence for the identified hazard and exposure."

New TSCA § 26(h) requires that, in carrying out § 6, "to the extent that the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science, and shall consider as applicable—

> (1) the extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information;
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> (2) the extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture;
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> (3) the degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented;
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> (4) the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and
>
> (5) the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models."

With regard to risk assessments completed prior to passage of the Lautenberg Act, including that for TCE, TSCA § 26(l)(4) provides that "the Administrator may publish proposed and final rules under section 6(a) that are consistent with the scope of the completed risk assessment for the chemical substance and consistent with other applicable requirements of section 6." Thus, EPA may base regulation on the pre-enactment risk assessments only to the extent that they comply with the substantive requirements above.

Regrettably, the proposal to ban TCE in aerosol degreasing addresses a broader scope of uses than considered in the Work Plan Assessment. The scope of that assessment is clear: "although the use of TCE as a solvent degreaser at large commercial/industrial operations is expected to be frequent and the concentration of TCE high, human exposures in these settings are expected to be monitored and controlled by Occupational Safety & Health Administration (OSHA); thus, this use is also not considered in this assessment" (p. 27). The Assessment is focused solely on exposure from TCE use as a solvent degreaser in small commercial settings and by consumers.[3] The proposed ban, however, recognizes no such limitation. It would prohibit commercial use of TCE for general aerosol degreasing, as well as its manufacture, processing, and distribution in commerce for this use. Because the proposed rule would ban uses beyond the scope of the underlying Work Plan Assessment, it is not "consistent with the scope of the completed risk assessment" and therefore does not comply with TSCA § 26(l)(4).

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[3] *See* Work Plan Assessment at Table 1-1.

Further, the proposed rule does not comply with the requirements of TSCA § 6(b)(4)(F) or TSCA § 26(h) and (i), which are expressly applicable to any EPA "decision based on science" under TSCA § 6. The disparity between the completed TCE Work Plan Assessment and the "applicable requirements of § 6" is obvious from a review of the procedures for risk evaluation under the amended TSCA proposed by EPA earlier this year.[4]

B. Deficiencies of Principal Non-Cancer Study

1. Not Reproducible

The Work Plan Assessment expressly relies on hazard values derived directly from a single academic study to estimate non-cancer risk.[5] Specifically, it states (p. 104):

> "The acute inhalation risk assessment used developmental toxicity data to evaluate the acute risks for the TSCA TCE use scenarios. As indicated previously, EPA's policy supports the use of developmental studies to evaluate the risks of acute exposures. This policy is based on the presumption that a single exposure of a chemical at a critical window of fetal development, as in the case of cardiac development, may produce adverse developmental effects (EPA, 1991).
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> "After evaluating the developmental toxicity literature of TCE, the TCE IRIS assessment concluded that the fetal heart malformations are the most sensitive developmental toxicity endpoint associated with TCE exposure (EPA, 2011e). Thus, EPA/OPPT based its acute risk assessment on the most health protective endpoint (i.e., fetal cardiac malformations; Johnson et al., 2003) representing the most sensitive human population (i.e., adult women of childbearing age and fetus >16 yrs).
>
> "The acute risk assessment used the PBPK-derived hazard values (HEC_{50}, HEC_{95}, or HEC_{99}) from Johnson et al. (2003) developmental study for each degreaser and spot cleaner use scenario. . . . These extremely low values result in margin of exposure ("MOE") values below 10 for almost all the occupational and residential exposure scenarios examined."

A single flawed study should not be the basis for the toxicological value that serves as the basis for regulation. Several other studies, including three GLP-compliant studies conducted under EPA guidelines to support pesticide registration (40 CFR § 870.3700) and Organization for Economic Coordination & Development ("OECD") guidelines (414) have been unable to reproduce the effect seen by Johnson *et al.* (2003).

Johnson *et al.* (2003) reported cardiac effects in rats from research carried out at the University of Arizona and originally published ten years earlier by the same authors.[6] In the earlier-published study, there was no difference in the percentage of cardiac abnormalities in rats dosed during both pre-mating

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[4] 82 Fed. Reg. 7562 (Jan. 19, 2017).

[5] Johnson PD, *et al.*, Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat, Environ Health Perspect. 111:289-92 (2003).

[6] Dawson, B, *et al.*, Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water, J. Am. Coll. Cardiol. 21: 1466-72 (1993).

and pregnancy at drinking water exposures of 1100 ppm (9.2%) and 1.5 ppm (8.2%), even though there was a 733-fold difference in the concentrations. The authors reported that the effects seen at these exposures were statistically higher than the percent abnormalities in controls (3%). For animals dosed only during the pregnancy period, the abnormalities in rats dosed at 1100 ppm (10.4%) were statistically higher than at 1.5 ppm (5.5%), but those dosed at 1.5 ppm were not statistically different from the controls. Thus, no meaningful dose-response relationship was observed in either treatment group. Johnson *et al.* republished in 2003 data from the 1.5 and 1100 ppm dose groups published by Dawson *et al.* in 1993 and pooled control data from other studies, an inappropriate statistical practice, to conclude that rats exposed to levels of TCE greater than 250 ppb during pregnancy have increased incidences of cardiac malformations in their fetuses.

2. Criticism in Literature and by Other Regulators

Johnson *et al.* (2003) has been heavily criticized in the published literature.[7] Indeed, its predecessor study was expressly rejected as the basis for MRLs by the Agency for Toxic Substances & Disease Registry (ATSDR) in its last TCE Toxicological Profile Update.[8] Moreover, the Johnson *et al.* (2003) findings were not reproduced in a study designed to detect cardiac malformations; this despite employing an improved method for assessing cardiac defects and the participation of Dr. Johnson herself.[9] No increase in cardiac malformations was observed in the second guideline study,[10] despite high inhalation doses and techniques capable of detecting most of the malformation types reported by Johnson *et al.* (2003). The dose-response relationship reported in Johnson *et al.* (2003) for doses spanning an extreme range of experimental dose levels is considered by many to be improbable, and has not been replicated by any other laboratory.[11]

Even the California Office of Environmental Health Hazard Assessment (OEHHA) rejected the study as deficient:

> "Johnson et al. (2003) reported a dose-related increased incidence of abnormal hearts in offspring of Sprague Dawley rats treated during pregnancy with 0, 2.5 ppb, 250 ppb, 1.5 ppm, and 1,100 ppm TCE in drinking water (0, 0.00045, 0.048, 0.218, and 128.52 mg/kg-day, respectively). The NOAEL for the Johnson study was reported to be 2.5 ppb (0.00045 mg/kg-day) in this short exposure (22 days) study. The percentage of abnormal hearts in the control group was 2.2 percent, and in the treated groups was 0 percent (low dose), 4.5 percent (mid dose 1), 5.0 percent (mid dose 2), and 10.5 percent (high dose).

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[7] Hardin, B, *et al.*, Trichloroethylene and cardiac malformations, Environ. Health Perspect. 112: A607-8 (2004); Watson, R., *et al.,* Trichloroethylene-contaminated drinking water and congenital heart defects: a critical analysis of the literature, Repro. Toxicol. 21: 117-47 (2006).

[8] ATSDR concluded that "[t]he study is limited in that only two widely spaced exposure concentrations were used and that a significant dose-response was not observed for several exposure scenarios." Toxicological Profile for Trichloroethylene Update (September 1997), at 88.

[9] Fisher, J, *et al.*, Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: do they affect fetal rat heart development? Int. J. Toxicol. 20: 257-67 (2001).

[10] Carney, E, *et al.*, Developmental toxicity studies in Crl:Cd (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene, Birth Defects Research (Part B) 77: 405–412 (2006).

[11] "Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a 'specific' cardiac teratogen." Hardin, B, *et al.*, Trichloroethylene and cardiac malformations, Environ. Health Perspect. 112: A607-8 (2004).

The number of litters with fetuses with abnormal hearts was 16.4 percent, 0 percent, 44 percent, 38 percent, and 67 percent for the control, low, mid 1, mid 2, and high dose, respectively. The reported NOAEL is separated by 100-fold from the next higher dose level. The data for this study were not used to calculate a public-health protective concentration since a meaningful or interpretable dose-response relationship was not observed. *These results are also not consistent with earlier developmental and reproductive toxicological studies done outside this lab in mice, rats, and rabbits: The other studies did not find adverse effects on fertility or embryonic development, aside from those associated with maternal toxicity (Hardin et al., 2004).*"[12]

3. Reservations of EPA Scientific Staff

Remarkably, an EPA staff review that was placed in the docket for the Work Plan Assessment reflects similar concerns. First, one staff member dissented over relying at all on the Arizona study:

"The rodent developmental toxicology studies conducted by Dawson et al. (1993), Johnson et al. (2003), and Johnson et al. (1998) that have reported cardiac defects resulting from TCE (and metabolite) drinking water exposures have study design and reporting limitations. Additionally, two good quality (GLP) inhalation and gavage rodent studies conducted in other laboratories, Carney et al. (2006) and Fisher et al. (2001), respectively, have not detected cardiac defects. These limitations and uncertainties were the basis of the single dissenting opinion of a team member regarding whether the database supports a conclusion that TCE exposures during development are likely to cause cardiac defects."[13]

Second, even the EPA staff that agreed with use of the study had little confidence that it supported the dose-response assessment:

"[A] majority of the team members agreed that the Johnson et al. (2003) study was suitable for use in deriving a point of departure. However, confidence of team members in the dose response evaluation of the cardiac defect data from the Johnson et al. (2003) study was characterized as between 'low' and 'medium' (with 7 of 11 team members rating confidence as 'low' and four team members rating confidence as 'low to medium')."[14]

It is surprising that EPA would consider use of a dose-response value for regulation from a study in which seven of its own scientists expressed "low" confidence, and in which the other four could muster no more than "low to medium" confidence. The same report notes: "In conclusion, there has not been a confirmation of the results of the Johnson et al. (2003) and Dawson et al. (1993) studies by another laboratory, but there has also not been a repeat of the exact same study design that would corroborate or refute their findings."

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[12] California EPA Public Health Goal for Trichloroethylene in Drinking Water (July 2009), at 21 (emphasis added).

[13] TCE Developmental Cardiac Toxicity Assessment Update (available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2012-0723-0045).

[14] *Id.*

4. EPA's Dose-Response Evaluation using Johnson *et al.* (2003) Is Inappropriate

The TCE Work Plan Assessment relies on the prior IRIS Assessment's evaluation of the relationship between TCE exposure dose and the development of cardiac defects, as described in Johnson *et al.* (2003). Ignoring for the moment the myriad of methodological deficiencies in the paper, a closer look at EPA's evaluation of that dose-response relationship in generating a point of departure (POD) raises several concerns. The importance of this activity cannot be overstated, as according to a paper published by the authors of the IRIS Assessment, Johnson *et al.* (2003) represents "the only available study potentially useable for dose-response analysis of fetal cardiac defects."[15]

In discussing the dose-response evaluation, Makris *et al.* (2016) further state that "[g]iven the uncertainties in the dose-response analysis related to the nature of the data, the confidence in the POD based on Johnson *et al.* (2003) has limitations. Overall, however, the POD derived in the 2011 TCE assessment (U.S. EPA, 2011), which used an approach consistent with standard U.S. EPA dose-response practices, remains a reasonable choice." It should be noted that, in order to achieve a better model fit in its derivation of a POD, EPA dropped the highest exposure dose from Johnson *et al.* (2003). With already questionable data, and no expectation that the highest dose of TCE would result in a diminished response, that decision should be reconsidered.

Makris *et al.* (2016) describe additional dose-response analyses performed to characterize the uncertainty in the POD. In summarizing the results of this analysis, they state that "[a]lternative PODs were derived based on use of alternative models, alternative BMR levels, or alternative procedures (such as LOAEL/NOAEL approach), each with different strengths and limitations. These alternatives were within *about an order of magnitude of the POD derived in the 2011 TCE assessment*" (emphasis added). This level of uncertainty in modeling the POD when combined with the uncertainty in the PBPK modeling (discussed elsewhere) and the overall poor quality of the underlying developmental toxicity study provide little confidence in the resulting non-cancer toxicological value in the Work Plan Assessment that drives the proposed regulation.

5. Reliance on Johnson *et al.* (2003) Is Inconsistent with Use of Best Available Science

All acute inhalation exposures in the TCE Work Plan Assessment were measured against potential developmental toxicity endpoints based solely on EPA's IRIS evaluation of Johnson *et al.* (2003). When HSIA requested access to the data used by EPA in its evaluation of the dose-response relationship between TCE exposure and cardiac defects reported in Johnson *et al.* (2003), the Agency provided the spreadsheet, referenced as Johnson (2009) (HERO ID 783484) in the 2011 IRIS Assessment, and indicated that was the entirety of the data evaluated. Examination of that spreadsheet reveals an absence of certain critical information, including, most importantly, dates for any of the individual treatment/control animals.

Acknowledging the documented deficiencies in their paper (and the data provided to EPA), the authors published an erratum aimed at updating the public record regarding methodological issues for Johnson *et al.* (2003).[16] According to Makris *et al.* (2016):

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[15] Makris SL, Scott CS, Fox J, *et al.*, Systematic evaluation of the potential effects of trichloroethylene exposure on cardiac development. Repro Toxicol (2016); http://dx.doi.org/10.1016/j.reprotox.2016.08.014

[16] Johnson PD, Goldberg SJ, Mays MZ, Dawson BV, Erratum: Erratum for Johnson *et al.* [Environ Health Perspect 113: A18 (2005)]; Environ Health Perspect 122: A94 (2014); http://dx.doi.org/10.1289/ehp.122-A94

"some study reporting and methodological details remain unknown, *e.g.*, the precise dates that each individual control animal was on study, maternal body weight/food consumption and clinical observation data, and the detailed results of analytical chemistry testing for dose concentration. Additional possible sources of uncertainty identified for these studies include that the research was conducted over a 6-yr period, that combined control data were used for comparison to treated groups, and that exposure characterization may be imprecise because tap (rather than distilled) drinking water was used in the Dawson *et al.* (1993) study and because TCE intake values were derived from water consumption measures of group-housed animals."

HSIA submits that the information contained in the above paragraph alone should disqualify Johnson *et al.* (2003) as "best available science" as required under EPA's proposed procedures for chemical risk evaluation under TSCA as amended.[17]

6. Failure to Conform to EPA Guidelines for Developmental Toxicity Risk Assessment

EPA's Guidelines for Developmental Toxicity Risk Assessment establish the framework for evaluation of developmental toxicity risk on a case-by-case basis.[18] Under these Guidelines, "[i]f data are considered *sufficient* for risk assessment, an oral or dermal reference dose for developmental toxicity (RfD_{DT}) or an inhalation reference concentration for developmental toxicity (RfC_{DT}) is then derived for comparison with human exposure estimates" (emphasis added).

In defining sufficiency, the Guidelines state: "In the case of animal data, agents that have been tested adequately in laboratory animals *according to current test guidelines* generally would be included in the "Sufficient Experimental Animal Evidence/Limited Human Data" category (emphasis added)." Where, as here, the "database on a particular agent includes less than the minimum sufficient evidence (as defined in the 'Insufficient Evidence' category) necessary for a risk assessment, but some data are available, this information could be used to determine the need for additional testing. . . . In some cases, a database may contain conflicting data. In these instances, the risk assessor must consider each study's strengths and weaknesses within the context of the overall database in an attempt to define the strength of evidence of the database for assessing the potential for developmental toxicity."

Given the demonstrated shortcomings of Johnson *et al.* (2003), which was not conducted to EPA test guidelines, and the availability to EPA of three guideline studies, we submit that the Guidelines for Developmental Toxicity Risk Assessment and TSCA §§ 6 and 26 require a weight of evidence evaluation of the database before EPA relies on Johnson *et al.* (2003) for regulatory purposes.

7. New Relevant Information

A third guideline study of TCE developmental toxicity has been sponsored by HSIA. The study was designed with a focus on cardiac abnormalities and included toxicokinetic measures to enable comparison with the earlier studies. It was intended to fill the remaining gap for a guideline study by the drinking water route, the same exposure route as Johnson *et al.* (2003). Regrettably, although the in-life

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[17] 82 Fed. Reg. 7562 (Jan. 19, 2017).

[18] 56 Fed. Reg. 63798 (December 5, 1991).

portion of the study was conducted during October and November, 2016, the concentrations of TCE measured in the drinking water solutions were found to be below the acceptable target range of 100% ± 10%, invalidating the study. The laboratory is conducting additional studies to identify the source of the deviations and the study will be rerun as soon as the dosing methodological issues are resolved and scheduling permits. A statement to this effect is attached as Appendix 1.

C. Deficiencies of Cancer Risk Assessment

1. Erroneous Characterization of TCE as "Carcinogenic to Humans"

While acute risks of developmental toxicity are characterized by EPA as of the greatest concern, the Work Plan Assessment also concludes that all but one of the degreaser exposure scenarios exceeded all the target cancer levels. The discussion of carcinogenicity in the Work Plan Assessment suffers from slavish reliance on EPA's earlier assessment of TCE under its Integrated Risk Information System.[19] The IRIS Assessment classifies TCE as "Carcinogenic to Humans." It fails to discuss (or even to recognize) that such classification is inconsistent with a definitive report by the National Academy of Sciences, discussed below.[20] We briefly address below how the epidemiological data on TCE do not meet the threshold for classification as "Carcinogenic to Humans."

a. Guidelines for Carcinogen Risk Assessment

EPA's 2005 Guidelines for Carcinogen Risk Assessment provide the following descriptors as to the weight of evidence for carcinogenicity:

- Carcinogenic to humans,
- Likely to be carcinogenic to humans,
- Suggestive evidence of carcinogenicity,
- Inadequate information to assess carcinogenic potential, and
- Not likely to be carcinogenic to humans.[21]

According to the Guidelines, "carcinogenic to humans" means the following:

"This descriptor indicates strong evidence of human carcinogenicity. It covers different combinations of evidence.

- "This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.

[19] "Toxicological Review of Trichloroethylene (CAS No. 79-01-6) in Support of Summary Information on the Integrated Risk Information System (IRIS)" ("IRIS Assessment")

[20] National Research Council, Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects (2009) (hereinafter "Camp Lejeune report").

[21] 70 Fed. Reg. 17766-817 (April 7, 2005).

- "Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when *all* of the following conditions are met: (a) There is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, *and* (b) there is extensive evidence of carcinogenicity in animals, *and* (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, *and* (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information. In this case, the narrative includes a summary of both the experimental and epidemiologic information on mode of action and also an indication of the relative weight that each source of information carries, *e.g.*, based on human information, based on limited human and extensive animal experiments."

According to the Guidelines, the descriptor "likely to be carcinogenic to humans":

"is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor 'Carcinogenic to Humans.' Adequate evidence consistent with this descriptor covers a broad spectrum. . . . Supporting data for this descriptor may include:

"An agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer:

- "An agent that has tested positive in animal experiments in more than one species, sex, strain, site or exposure route, with or without evidence of carcinogenicity in humans;

- "A positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy or an early age at onset;

- "A rare animal tumor response in a single experiment that is assumed to be relevant to humans; or

- "A positive tumor study that is strengthened by other lines of evidence."

According to the Guidelines, the descriptor "suggestive evidence of carcinogenicity":

"is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species. Depending on the extent of the database, additional studies may or may not provide further insights. Some examples include:

- "A small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor 'Likely to Be Carcinogenic to Humans;'

- "A small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed;

- "Evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence; or

- "A statistically significant increase at one dose only, but no significant response at the other doses and no overall trend."

b. Application of the Guidelines to TCE

In considering the data in the context of applying the "Carcinogenic to Humans" descriptor, one first considers the weight of the epidemiological evidence. We judge the epidemiologic evidence to be neither "convincing" nor "strong," two key terms in the Guidelines. This judgment is based on four recent reviews and meta-analyses of occupational TCE exposures and cancer as well as other reviews of this literature.[22] The recent review and meta-analysis by Kelsh *et al.* focuses on occupational TCE exposure and kidney cancer, and includes the Charbotel *et al.* study that is emphasized in the IRIS and Work Plan Assessments.[23] Both the EPA meta-analysis and the Kelsh *et al.* meta-analysis of the TCE kidney cancer epidemiologic literature produced similar summary results. However in Kelsh *et al.* the limitations of this body of research, namely exposure assessment limitations, potential unmeasured confounding, potential selection biases, and inconsistent findings across groups of studies, did not allow for a conclusion that there is sufficient evidence of a causal association, despite a modest overall association.

There are reasonably well-designed and well-conducted epidemiologic studies that report no association between TCE and cancer, some reasonably well-designed and conducted studies that did report associations between TCE and cancer, and finally some relatively poorly designed studies reporting both positive and negative findings. Overall, the summary relative risks or odds ratios in the meta-analysis studies (EPA or published meta-analyses) generally ranged between 1.2 and 1.4. The draft assessment refers to these associations as "small," a term not

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[22] Alexander, D, *et al.*, A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukaemia, Occup Med (Lond) 56:485–493 (2006); Alexander, D, *et al.*, A meta-analysis of occupational trichloroethylene exposure and liver cancer, Int Arch Occup Environ Health 81(2):127–43 (2007); Mandel, J, *et al.*, Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review, Occup Environ Med 63:597–607 (2006); Kelsh, M, *et al.*, Occupational trichloroethylene exposure and kidney cancer: a meta-analysis, Epidemiology 21(1): 95-102 (January 2010).

[23] Charbotel, B, *et al.*, Case-control study on renal cell cancer and occupational exposure to trichloroethylene, Part II: Epidemiological aspects, Ann Occup Hyg 50(8):777–787 (2006).

typically consistent with "convincing" and "strong." Weak or small associations may be more likely to be influenced by or be the result of confounding or bias. Smoking and body mass index are well-established risk factors for kidney cancer, and smoking and alcohol are risk factors for liver cancer, yet the potential impact of these factors on the meta-analysis associations was not fully considered. There were suggestions that these factors may have impacted findings (*e.g.,* in the large Danish cohort study of TCE exposed workers, the researchers noted that smoking was more prevalent among the TCE exposed populations, however little empirical data were provided). In addition, co-linearity of occupational exposures (*i.e.,* TCE exposure correlated with chemical and/or other exposures) may make it difficult to isolate potential effects of TCE from those of other exposures within a given study, and hinder interpretation across studies. For example, although Charbotel *et al.* reported potential exposure response trends, while controlling for many confounders of concern (which strengthens the weight of evidence), they also reported attenuated associations for cumulative TCE exposure after adjustment for exposure to cutting fluids and other petroleum oils (weakening the weight of the evidence). This study is also limited due to other potential study design considerations such as selection bias, self reporting of work histories, and residual confounding.

When examining the data for TCE and non-Hodgkin lymphoma, kidney cancer, and liver cancer, associations were inconsistent across occupational groups (summary results differed between aerospace/aircraft worker cohorts compared with workers from other industries), study design, location of the study, quality of exposure assessment (*e.g.,* evaluating studies that relied upon biomonitoring to estimate exposure *vs.* semi-quantitative estimates *vs.* self-report, etc.), and by incidence *vs.* mortality endpoints. Although EPA examined high dose categories, it did not evaluate any potential dose-response relationships across the epidemiologic studies (except for Charbotel *et al.*). Reviews of the epidemiologic data reported in various studies for different exposure levels (*e.g.,* cumulative exposure and duration of exposure metrics) did not find consistent dose-response associations between TCE and the three cancer sites under review.[24] An established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature. Thus, based on an overall weight of evidence analysis of the epidemiologic research, these data do not support the conclusion that there is "strong" or "convincing" evidence of a causal association between human exposure and cancer.

EPA's Guidelines also state that a chemical may be described as "Carcinogenic to Humans" with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence, all of which must be met. One of these lines of evidence is "extensive evidence of carcinogenicity in animals." Therefore, we must briefly evaluate the animal data.

The criteria that have to be met for animal data to support a "carcinogenic to humans" classification are stated in a sequential manner with an emphasized requirement that all criteria have to be met. Since the Guidelines consider this to be an "exceptional" route to a "carcinogenic to humans" classification, we would expect rigor to have been applied in assessing animal data against the criteria. This simply was not done.

Of the four primary tissues that EPA evaluated for carcinogenicity, only one or perhaps two rise to the level of biological significance. Discussion of the remaining tumor types appears to presuppose

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[24] Mandel, J, *et al.*, Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review, Occup Environ Med 63:597–607 (2006); Alexander, D, *et al.*, A meta-analysis of occupational trichloroethylene exposure and liver cancer, Int Arch Occup Environ Health 81(2):127–43 (2007); Kelsh, M, *et al.*, Occupational trichloroethylene exposure and kidney cancer: a meta-analysis, Epidemiology 21(1): 95-102 (January 2010).

that TCE is carcinogenic. The resulting discussion appears then to overly discount negative data, of which there are many, and to highlight marginal findings. The text does not appear to be a dispassionate rendering of the available data. Specifically, EPA's conclusion that kidney cancer is evident in rats rests on *one* statistically significant finding in over 70 dose/tumor endpoint comparisons and references to exceedances of historical control values.[25] Using a 0.05 p-value for statistical significance, a frequency of 1 or even several statistically or biologically significant events is expected in such a large number of dosed/tumor groups. EPA's overall conclusion based on these flawed studies cannot be that TCE is a known kidney tumorigen. The best that can be said is that the data are inconsistent. Certainly they do not meet the criterion of "extensive evidence of carcinogenicity in animals." Several marginal findings do not constitute "extensive evidence."

For all these reasons, EPA's classification of TCE as "Carcinogenic to Humans" is not supported by the evidence and cannot be justified under the 2005 Guidelines.[26]

c. EPA's Position that there is 'Convincing Evidence' that TCE Is Carcinogenic to Humans is Inconsistent with National Academy of Sciences Conclusion of only 'Limited or Suggestive Evidence'

The IRIS Assessment states that "TCE is characterized as 'carcinogenic to humans' by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer."

Box 2 of the Academy's Camp Lejeune report, attached as Appendix 3, categorizes every cancer outcome reviewed in relation to exposure to TCE, the dry cleaning solvent perchloroethylene, or a mixture of the two. The categories are taken directly from a respected Institute of Medicine (IOM) report.[27] These categories are "sufficient evidence of a causal relationship," "sufficient evidence of an association," "limited or suggestive evidence of an association," "inadequate evidence to determine an association," and "limited or suggestive evidence of no association," all as defined in Box 1, also attached.

Looking at Box 2, evidence considered by EPA to be "convincing evidence of a causal association between TCE exposure in humans and kidney cancer" would seem to be considered "sufficient evidence of a causal relationship." Yet the Academy found no outcomes in that category. It would at least be "sufficient evidence of an association." Again, the Academy found no outcomes in that category. Only in the third category, "limited or suggestive evidence of an association," does one find kidney or any other cancer outcome associated with TCE.

"Limited evidence of an association" is far from "convincing evidence of causation." One would expect at the least a detailed explanation of EPA's very different conclusion. Although the 2009 Camp Lejeune study was already published, and indeed is cited in the references, there is no mention of it in the text of the IRIS Assessment, even though the previous draft had just been the subject of a multi-year review by the Academy.

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[25] And that bioassay is from a laboratory whose studies EPA has reviewed and declined to rely upon in other assessments.

[26] Further commentary to this effect, provided by a distinguished group of consultants in connection with the TCE IRIS Assessment but not addressed by EPA, is attached as Appendix 2.

[27] Institute of Medicine, Gulf War and Health, Vol. 2, Insecticides and Solvents (National Academies Press) (2003).

The Camp Lejeune committee began with a comprehensive review of the epidemiology studies of the two solvents by the IOM for its Gulf War Report. They then identified new studies published from 2003 to 2008 and considered whether these changed the conclusions in the IOM report. In the case of TCE and kidney cancer, this was the case. The Camp Lejeune committee considered six new cohort studies and two case-control studies (including Charbotel *et al.*). They concluded that several of these studies reported an increased risk of kidney cancer, but observed that the results were often based on a relatively small number of exposed persons and varied quality of exposure data and methodology. Given these data, the committee raised the classification for TCE to match the IOM conclusion of "limited" evidence for perchloroethylene.

EPA, on the other hand, offered the summary conclusion of convincing human evidence, based on the "consistency" of increased kidney cancer across the different studies. The authors of these studies, however, do not agree with EPA's characterization of them. For example, the authors of Charbotel *et al.*, the study EPA finds most compelling, state that the "study suggests an association between exposures to high levels of TCE and increased risk of [renal cell carcinoma]. Further epidemiological studies are necessary to analyze the effect of lower levels of exposure."

Given the flaws in the IRIS Assessment, and the very different conclusion reached by the Academy in its Camp Lejeune report on the same body of data, the Work Plan Assessment should not rely on the IRIS Assessment's classification of TCE as "Carcinogenic to Humans."

2. EPA Should Reassess Available Cancer Epidemiology Data, Given Publication of More Recent and Larger Studies on Worker Populations

The observation of an elevated but weak kidney cancer association reported by Charbotel *et al.* (2006)[28] contrasts with other occupational studies which did not find an elevation in kidney cancer in industries using TCE as a metal degreaser, *e.g.*, aircraft manufacturing, metal cleaning, etc., where exposures may be higher than for screw cutters. Lipworth and coworkers (2011) found no evidence of increased kidney cancer in a large worker cohort with multiple decades of TCE exposure and extended cancer follow-up evaluations.[29] The aircraft manufacturing study involved a total cohort of 77,943 workers, of which 5,443 were identified as exposed to TCE. The study involved evaluations from 1960 through 2008, at which time 34,248 workers had died. Approximately 30% of the workers were hired before 1960 (60% born before 1940), 52% terminated employment by 1980, and approximately a third of the workers were employed for more than 20 years. The standardized incidence ratio (SIR) for kidney cancer in the TCE-exposed workers was reported as 0.66 (CI 95%: 0.38-1.07). This value for the SIR indicates that these workers were potentially less likely to get kidney cancer than the normal population (or at least had the same rate as the normal population – SIR of 1).

More recently, two large Nordic country epidemiological studies, both of which had extensive follow-up of the cohorts, have likewise failed to find an association between TCE and kidney cancer. An SIR of 1.01 (0.70-1.42) was found by Hansen *et al.* (2013) for kidney cancer based on 32 cases out of a total of 997 cancer cases in a cohort of 5,553 workers in Finland, Sweden, and Denmark, indicating that

[28] Charbotel, B, *et al.*, Case-control study on renal cell cancer and occupational exposure to trichloroethylene, Part II: Epidemiological aspects, Ann Occup Hyg 50(8):777–787 (2006).

[29] Lipworth L, Sonderman JS, Mumma MT, *et al.*, Cancer mortality among aircraft manufacturing workers: an extended follow-up, J Occup Environ Med 53(9): 992-1007 (2011).

rates were the same as the normal population.[30] TCE exposures in this cohort were directly confirmed from urinary biomonitoring of the TCE metabolite trichloroacetic acid (TCA). However, overall TCE exposures were likely low in this cohort in that most urinary TCA measurements were less than 50 mg/L, corresponding to approximately 20 ppm TCE exposure. Thus, consistent with the conclusions of Bruning *et al.* (2003),[31] this study indicates TCE is unlikely to be a low-dose kidney carcinogen.

Similarly, no evidence of kidney cancer was found by Vlaanderen *et al.* (2013) in a recent follow-up examination of the Nordic Occupational Cancer cohort (Finland, Iceland, Norway, Sweden) in which statistically non-significant risk ratios (RR) of 1.01 (0.95-1.07), 1.02 (0.97-1.08), and 1.00 (0.95-1.07) were reported for a total of 4,145 renal cancer cases approximately equally distributed across three respective TCE exposure groups (tertiles) assigned from a job exposure matrix analysis.[32] Finally, although a meta-analysis of 23 studies meeting criteria for study inclusion found a slightly increased simple summary association of TCE and kidney cancer, RR 1.42 (1.17-1.77), more detailed analyses of subgroups suggested no association, or possibly a moderate elevation in kidney cancer risk, and no evidence of increasing risk with increasing exposure.[33]

These more recent studies were not reviewed in the 2011 TCE IRIS Assessment or the 2014 TCE Work Plan Assessment that form the basis for the proposed regulation. Any regulatory action under TSCA § 6, however, is required to be based on the "best available science" supported by "substantial evidence in the record." This provides compelling support for our position that the instant proposal should be withdrawn and the uses under consideration be examined following the TCE assessment EPA will be conducting in the near future under TSCA § 6(b)(4)(A).

3. EPA's Reliance on Charbotel *et al.* (2006) Results in an Overly Conservative Estimate of Risk

In its 2014 Work Plan Assessment of potential cancer risk, EPA focused solely on inhalation exposures and relied on an inhalation unit risk (IUR) value developed in the 2011 IRIS Assessment. The IUR was based primarily on epidemiology data from the case-control study on renal cell carcinoma (RCC) by Charbotel *et al.* (2006), discussed above. Although other epidemiological studies were used to derive an adjusted IUR estimate for the combined risk of developing RCC, NHL, or liver cancer, EPA concedes a lower level of confidence in both the NHL and liver cancer databases. While the Charbotel *et al.* study suggests a relationship between cumulative TCE exposure and RCC incidence, the reliability of the exposure estimates is a major concern.

The National Academy of Sciences Committee that reviewed the draft IRIS assessment released in 2001 recommended that:

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[30] Hansen J, Sallmén M, Seldén AI, *et al.*, Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies, J Natl Cancer Inst 105(12): 869-877 (2013).

[31] Brüning T, Pesch B, Wiesenhütter B, *et al.*, Renal cell cancer risk and occupational exposure to trichloroethylene: Results of a consecutive case-control study in Arnsberg, Germany, Am J Ind Med. 43(3): 274-285 (2003).

[32] Vlaanderen J, Straif K, Pukkala E, *et al.*, Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries, Occup Environ Med 70(6): 393-401 (2013).

[33] Kelsh MA, Alexander DD, Mink PJ, Mandel JH, Occupational trichloroethylene exposure and kidney cancer: a meta-analysis, Epidemiology 21(1): 95-102 (2010).

> "[t]here appear to be insufficient epidemiologic data to support quantitative dose-response modeling for trichloroethylene and cancer. The committee recommends that toxicologic data be used to fit the primary dose-response model(s) and that the available epidemiologic data be used only for validation. The committee does not believe that the available information is sufficient to determine the best dose-response model for trichloroethylene."[34]

EPA should follow the recommendation of the National Academy of Sciences, which referenced the Charbotel *et al.* (2005) final study report in its review of TCE.[35] The authors' own conclusions that the study only "suggests that there is a weak association between exposures to TRI [TCE] and increased risk of RCC" argues against the existence of the robust relationship which should be required for a dose-response assessment used as the basis for regulation.[36]

The exposure assessment for the Charbotel study was based on questionnaires and expert judgment, not direct measures of exposure.[37] Worker exposure data from deceased individuals were included in the study. In contrast to living workers, who were able to respond to the questionnaires themselves, exposure information from deceased workers (22.1% of cases and 2.2% of controls) was provided by surviving family members. The authors acknowledge that "this may have led to a misclassification for exposure to TCE due to the lower levels in the quality of information collected."

Analysis of the data revealed evidence of confounding from cutting fluid exposure. Unfortunately, TCE and cutting oil were co-exposures that could not be disaggregated and the majority of

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[34] National Research Council, Assessing the human health risks of trichloroethylene: key scientific issues, National Academies Press, Washington, DC (2006); http://www.nap.edu/openbook.php?record_id=11707&page=R1.

[35] Charbotel B, Fevotte J, Hours M, *et al.*, Case-control study on renal cell cancer and occupational trichloroethylene exposure, in the Arve Valley (France), Lyon, France: Institut Universitaire de Médecine du Travail, UMRESTTE, Université Claude Bernard (2005); http://hal.archives-ouvertes.fr/docs/00/54/59/80/PDF/charbotel_octobre_05.pdf

[36] This concern was recognized by the European Chemicals Agency (ECHA) in its 2013 Chemical Safety Report on TCE: "[T]here are several concerns with this study that should be taken into consideration when assessing its use in risk assessment and hazard characterization. For example, potential selection bias, the quality of the exposure assessment, and the potential confounding due to other exposures in the work place. With respect to the potential for selection bias, no cancer registry was available for this region to identify all relevant renal cell cancer cases from the target population. Case ascertainment relied on records of local urologists and regional medical centers; therefore, selection bias may be a concern. Given the concerns of the medical community in this region regarding renal cell cancer (RCC) among screw cutting industry workers, it is likely that any cases of renal cell cancer among these workers would likely be diagnosed more accurately and earlier. It is also much more unlikely that an RCC case among these workers would be missed compared to the chance of missing an RCC case among other workers not exposed to TCE. This preference in identifying cases among screw-cutting industry workers would bias findings in an upward direction. Concerning the potential for other exposures that could have contributed to the association, screw-cutting industry workers used a variety of oils and other solvents. Charbotel *et al.* reported lower risks for TCE exposure and renal cell cancer once data were adjusted for cutting oils. In fact, they noted, 'Indeed many patients had been exposed to TCE in screw-cutting workshops, where cutting fluids are widely used, making it difficult to distinguish between cutting oil and TCE effects.' This uncertainty questions the reliability of using data from Charbotel *et al.* since one cannot be certain that the observed correlation between kidney cancer and exposure is due to trichloroethylene."

[37] Fevotte J, Charbotel B, Muller-Beauté P, *et al.*, Case-control study on renal cell cancer and occupational exposure to trichloroethylene, Part I: Exposure assessment, Ann Occup Hyg 50: 765-775 (2006); http://dx.doi.org/10.1093/annhyg/mel040.

the TCE exposed population, the screw cutters, could be expected to experience similar patterns of exposure for both TCE and cutting fluids (probably in aerosol form). Thus the apparent dose-response relationship for TCE could be wholly or in part the result of exposure to cutting fluids.

In their 2006 publication of the study results, the authors assigned cumulative exposures into tertiles (i.e., low, medium and high), yet the dose-response evaluation conducted as part of the IRIS Assessment relied on mean cumulative exposure levels provided at a later date.[38] Although the IRIS Assessment references the email submission of the data to EPA, it provides no detail on the technical basis for the table, raising serious transparency issues.

In an apparent acknowledgement of the uncertainty of the exposure information, Charbotel *et al.* (2006) included an evaluation of "the impact of including deceased patients (proxy interviews) and elderly patients (>80 years of age)" on the relationship between exposure to TCE and RCC. Interestingly, it was stated that "only job periods with a high level of confidence with respect to TCE exposure were considered" in the study, an apparent reference to the use of two different occupational questionnaires, one "devoted to the screw-cutting industry and a general one for other jobs." As the Adjusted Odds Ratio (OR) for the high cumulative dose group was actually higher in the censored subgroup than in the uncensored group [3.34 (1.27-8.74) vs 2.16 (1.02-4.60)], the authors cavalierly suggested that "misclassification bias may have led to an underestimation of the risk."

What the authors and EPA appear to have overlooked is that, in addressing the misclassification bias, Charbotel may also have altered the cumulative dose-response relationship. For example, in the censored subgroup there were now only 16 exposed cases (1 in the Low Group, 4 in the Medium Group and 11 in the High Group) with Adjusted ORs of 0.85, 1.03 and 3.34, respectively. If the dose-response relationship in this higher-confidence subgroup has changed, use of the lower-confidence group to calculate the IUR would have to be rigorously justified by EPA before it could be considered sufficiently robust to drive the types of decisions based on unit risk that are found in the proposed rule.

4. Use of TCE Glutathione Conjugate Derived Metabolites Dichlorovinylglutathione (DCVG) and Dichlorovinylcysteine (DCVC) in TCE Renal Toxicity and Cancer Risk Assessment Should Be Reconsidered Given Improved Understanding of the Differential Quantitative Formation of these Metabolites in Animals Relative to the TCE Oxidative Metabolites Trichloroethanol (TCOH), Trichloroacetic Acid (TCA) and Dichloroacetic Acid (DCA)

The TCE IRIS Assessment relies in part on the conclusion that DCVG and DCVC, which are weakly active renal toxicants and genotoxicants, are formed in toxicologically significant concentrations following human exposures to TCE. Importantly, the basis for this conclusion rests on studies in which a relatively high blood DCVG concentration (100 nM) was observed in volunteers exposed for 4 hours to 50 or 100 ppm TCE.[39] However, Lash *et al.* (1999) relied on a colorimetric chromatographic method analysis of TCE glutathione conjugate-derived metabolites which had substantial potential for detection of non-TCE-specific endogenous substances. Subsequent radiochemical and HPLC-MS/MS based analyses that specifically quantitated both DCVG and DCVC have found that the activity of the

[38] Charbotel B (2008) [Email from Barbara Charbotel, University of Lyon, to Cheryl Scott, EPA].

[39] Lash LH, Putt DA, Identification of S-(1,2-dichlorovinyl)glutathione in the blood of human volunteers exposed to trichloroethylene, J Toxicol Env Hlth Part A, 56: 1-21 (1999).

glutathione conjugate pathway is substantially lower than that of the oxidative pathway resulting in TCA and DCA formation in both animals and humans.[40]

Since the publication of the TCE IRIS Assessment in 2011, additional studies have evaluated the kidney concentrations of TCE oxidative and glutathione conjugate-derived metabolites in a variety of mouse strains administered 5 daily oral 600 mg/kg doses of TCE.[41] Metabolites were quantitated 2 hr after the last daily dose in that toxicokinetic evaluations had shown the approximate maximum plasma concentrations of TCA, DCA, DCVG and DCVC were observed 2 hr following oral TCE treatment.[42] Using a structure-specific HPLC-ESI-MS/MS method, Yoo *et al.* (2015) demonstrated that DCVG and DCVC were only a very small fraction of total oxidative metabolites quantitated in kidney. TCOH kidney concentrations were 2-4-fold greater than TCA, and TCA concentrations were 100-1000 greater than DCA. Importantly, DCA concentrations were 100-1000-fold greater than DCVG and DCVC, resulting in the conclusion that TCE oxidative metabolism was up to 5 orders of magnitude greater than glutathione conjugate-derived metabolism. These findings were consistent with the earlier report from Kim *et al.* (2009) in which the plasma toxicokinetics TCA, DCA, DCVG and DCVC following a single 2140 mg/kg oral TCE dose found that the cumulative AUC of oxidative metabolites was 40,000-fold higher than the combined AUC of DCVG and DCVC; note that this study did not quantify TCOH, which would have further increased the disparity of glutathione conjugate-derived relative to oxidative-derived metabolites. These data demonstrate a dramatically lower function glutathione-conjugate metabolism relative to oxidative metabolism in mice, despite the observation by Dekant (2010) that mice generate DCVC at slightly higher rates than rats and greater than 10-fold higher than humans.

The results of studies using structure-specific analytical methods for quantitation of DCVG and DCVC directly challenge the hypothesis that glutathione conjugate-derived metabolites plausibly account for the genotoxicity, renal cytotoxicity, and ultimate carcinogenicity in rodents.[43] DCVC was only marginally cytotoxic (LDH release), if at all, when incubated at 0.2M (200,000 nM) with isolated renal cortical cells of male and female rats. This *in vitro* concentration is substantially higher than the approximate maximum kidney concentrations of 10-75 nM DCVC resulting from treatment of various strains of mice with a high oral TCE dose of 600 mg/kg/day for 5 days observed by Yoo *et al.* (2015). In addition, a likely NOAEL of 1 mg/kg/day was reported for kidney toxicity (no change in serum BUN, weak tubule dilation and no necrosis) in mice administered DCVC orally or intraperitoneally at 1, 10 or 30 mg/kg/day, 1 day per week, for 13 weeks.[44] If, based on Yoo *et al.* (2015), it is assumed that the ratio of formation of oxidative metabolites to glutathione conjugate-derived metabolites is 10,000:1, an implausibly high (occupational or general population) dose of 6044 mg/kg TCE would be required to

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[40] Dekant,W (2010), attached as Appendix 4.

[41] Yoo HS, Bradford BU, Kosyk O, Uehara T, Shymonyak S, Collins LB, Bodnar WM, Ball LM, Gold A, Rusyn I, Comparative analysis of the relationship between trichloroethylene metabolism and tissue-specific toxicity among inbred mouse strains: kidney effects, J Toxicol Env Hlth Pt A, 78: 32-49.b (2015).

[42] Kim, S, Kim, D, Pollack, GM, Collins, LB, and Rusyn, I, Pharmacokinetic analysis of trichloroethylene metabolism in male B6C3F1 mice: Formation and disposition of trichloroacetic acid, dichloroacetic acid, S-(1,2-dichlorovinyl)glutathione and S-(1,2-dichlorovinyl)-L-cysteine, Toxicol Appl Pharmacol 238: 90-99 (2009).

[43] Lash LH, Qian W, Putt DA, Hueni SE, Elfarra AA, Krause RJ, Parker JC, Renal and hepatic toxicity of trichloroethylene and its glutathione-derived metabolites in rats and mice: Sex-, species-, and tissue-dependent differences, J Pharmacol Exp Ther 297: 155-164 (2001).

[44]Shirai N, Ohtsuji M, Hagiwara K, Tomisara H, Ohtsuje N, Hirose S, Hagiwara H, Nephrotoxic effect of subchronic exposures to S-(1,2-dichlorovinyl)-L-cysteine in mice, J Toxicol Sci 37: 871-878.h (2012).

deliver a NOAEL dose of 1 mg/kg/day DCVC (1 mmol/kg/day TCE results in 0.0001 mmol/kg/day DCVC; 1 mg/kg/day DCVC = 0.0046 mmol/kg/day). These dose-toxicity calculations suggest that it appears toxicologically implausible that real-world exposures to TCE are capable of producing doses of DCVC sufficient to cause renal toxicity and carcinogenicity in mice.

D. Peer Review Ignored

The draft Work Plan Assessment was the subject of peer review by a panel selected by EPA in 2013. The peer review report highlights that it was a screening level assessment that inappropriately relied on an unreproducible study, and recommended that the assessment be abandoned.[45] One reviewer devoted six pages to a very detailed critique of Johnson *et al.* (2003) and EPA's reliance on such a deficient study.[46] Nevertheless, EPA ignored the peer review. Remarkably, even though the trade press article on the peer review was entitled *EPA Peer Reviewers Say Trichloroethylene Analysis Not Ready for Regulatory Use*, the EPA Assistant Administrator for Chemical Safety and Pollution Prevention wrote to the EPA Inspector General that "[i]t is notable that *the external peer reviews of all the Work Plan assessments we have completed thus far supported our overall assessment methodologies and conclusions*."[47] A more detailed description of the peer reviewers' comments is attached as Appendix 3.

Ppeer review is identified as a key step in EPA's proposed procedures for chemical risk evaluation under TSCA as amended. EPA states that "[i]n addition to any targeted peer review of specific aspects of the analysis, the entire risk assessment will also undergo peer review, as it is important for peer reviewers to consider how the various underlying analyses fit together to produce an integrated risk characterization which will form the basis of unreasonable risk determination."[48] As the draft Work Plan Assessment for TCE did not address the spot cleaning scenario at all, the assessment of risks under that scenario has *never* been subjected to peer review. Thus an applicable requirement of TSCA §§ 6 and 26(l)(4) for reliance on the Work Plan Assessment has not been met.

E. Screening Level Assessment

As noted above and in Appendix 5, the peer review report highlights that the Work Plan Assessment was a screening level assessment. Specifically, the Chairperson of EPA's peer review panel wrote:

> "The draft document fails to articulate satisfactorily that the analysis described within should be characterized as a screening level assessment. . . . I believe that the Agency acted prematurely in issuing this (screening level) assessment for public comment. . . . After listening carefully to the comments and contributions from the other members of

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[45] https://www.epa.gov/sites/production/files/2015-09/documents/tce_consolidated_peer_review_comments_september_5_2013.pdf.

[46] *Id.*

[47] Response to Office of Inspector General Draft Report No. OPE-FY14-0012 "EPA's Risk Assessment Division Has Not Fully Adhered to Its Quality Management Plan," (July 30, 2014), Appendix A, p.10 (available at https://www.epa.gov/sites/production/files/2015-09/documents/20140910-14-p-0350.pdf) (emphasis added). *Compare* BNA Daily Environment Report, *EPA Peer Reviewers Say Trichloroethylene Analysis Not Ready for Regulatory Use* (July 18, 2013).

[48] 82 Fed. Reg. at 7572.

the Panel, I have concluded that there would little benefit in revising this draft screening assessment."

With regard to aerosol degreasing, EPA identified only two aerosol degreasing products containing TCE in the marketplace and found no emissions or monitoring data for either product – thus these are hypothetical exposures. Further, EPA used E-FAST2/CEM modeling to develop "high-end acute inhalation exposure estimates" based solely on professional judgment, providing confirmation that this is a screening level assessment. The highest uncertainties were associated with mass of product used per event, duration of event, and number of events per year, as the values selected were hypothetical, thus leading to further lack of confidence in the assessment.

For spot cleaning workers the problems with the exposure assessment are even more obvious. A major limitation of the exposure assessment used to evaluate potential risk arising from spot cleaning operations was the unavailability of relevant exposure monitoring data. Section 2.4.2.5 of the Work Plan Assessment, however, references a study specific to spot cleaning and states that "site-specific parameters from this study were incorporated into the NF/FF model to obtain site-specific model estimates of worker exposure."[49]

Examination of the NIOSH (1997) study reveals that the air monitoring was actually conducted in response to an OSHA complaint from workers and the report states that "[c]onditions at this shop were probably worst case." Use of monitoring data from a worst case, potential enforcement situation adds additional strength to the concern that the Work Plan Assessment is actually a screening level assessment which does not reflect normal operating conditions and exposures.

It is clear that a risk evaluation that supports a TSCA § 6 rule must be more robust than the screening level Work Plan Assessment that EPA carried out for TCE, which does not comply with Office of Management and Budget ("OMB") guidelines implementing the Information Quality Act.[50] First, EPA must conduct a "highly influential scientific assessment" to support TSCA § 6 rulemaking. OMB defines a scientific assessment as "highly influential" if dissemination of the assessment could have a potential impact of more than $500 million in any one year on either the public or private sector, or if the dissemination is novel, controversial, precedent-setting, or has significant interagency interest.

The TCE assessment employed worst-case or default assumptions that led to overestimation of potential risks. Such assessments may be appropriate to support a decision that no further action or evaluation is necessary, because there is confidence that the potential risks are not a concern. However, they are inappropriate to support regulations intended to reduce risk because screening level assessments do not accurately estimate risk or quantify exposures. Second, OMB's guidelines also require agencies to subject highly influential scientific assessments to more rigorous peer review. For TCE, EPA selected a contractor to manage the peer review process, even though experts consider contractor-managed peer review to be the least rigorous level of peer review.

F. Summary of Concerns

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[49] National Institute for Occupational Safety and Health (NIOSH), Control of Health and Safety Hazards in Commercial Dry Cleaning, Publication Number 97-150, Centers for Disease Control and Prevention, Atlanta, GA (1997); http://www.cdc.gov/niosh/docs/97-150/#controls

[50] OMB, Final Information Quality Bulletin for Peer Review (Dec. 16, 2004) (available at https://www.whitehouse.gov/sites/default/files/omb/assets/omb/memoranda/fy2005/m05-03.pdf).

In sum, the TCE Work Plan Assessment is inconsistent with the applicable requirements of revised § 6 in the following ways, among others:

- It expressly relies on hazard values derived directly from a single academic study to estimate non-cancer risk, even though several other studies, including two GLP-compliant studies conducted under EPA guidelines, have been unable to reproduce the effect;[51]

- The University of Arizona study upon which EPA relies has been heavily criticized in the published literature,[52] and other regulatory agencies have expressly declined to rely on the academic study citing data quality concerns;[53]

- The authors of the Arizona study have published repeated corrections that fail to address the data quality concerns;[54] and a majority of EPA's own staff scientists expressed "low" confidence in its results.[55]

- The Work Plan Assessment relies on qualitative and quantitative estimates of cancer risk that are not realistic or justified by any underlying science. Two recent large Nordic epidemiological studies, both of which had extensive follow-up of the cohorts, failed to find an association between TCE and kidney cancer, but these are not addressed in the Work Plan Assessment. Further, EPA's reliance upon a potency factor based on Charbotel *et al.* (2006) directly contravenes the advice EPA received from the National Academy of Sciences

- For aerosol degreasing EPA provided no emissions or monitoring data – thus these are hypothetical exposures. The spot cleaning exposure assessment relies solely on a 2007 California study, which EPA recognized may not be representative of US dry cleaning facilities. The draft TCE Assessment, entitled "Degreaser and Arts/Crafts Uses," did not address spot cleaning at all (except to say that none of those sold to consumers contained TCE), but the final Work Plan Assessment is entitled "Degreasing, *Spot Cleaning* and Arts & Crafts Uses" and includes commercial use of TCE as a spotting agent at dry cleaning facilities.

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[51] *Compare* Johnson *et al.* (2003) to Fisher, J, *et al.*, Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: do they affect fetal rat heart development? Int. J. Toxicol. 20: 257-67 (2001) and Carney, E, *et al.*, Developmental toxicity studies in Crl:Cd (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene, Birth Defects Research (Part B) 77: 405–412 (2006).

[52] *E.g.*, "Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a 'specific' cardiac teratogen." Hardin, B, *et al.*, Trichloroethylene and cardiac malformations, Environ. Health Perspect. 112: A607-8 (2004); Watson, R., *et al.*, Trichloroethylene-contaminated drinking water and congenital heart defects: a critical analysis of the literature, Repro. Toxicol. 21: 117-47 (2006).

[53] *E.g.*, "The data from this study were not used to calculate a public-health protective concentration since a meaningful or interpretable dose-response relationship was not observed. These results are also not consistent with earlier developmental and reproductive toxicological studies done outside this lab in mice, rats, and rabbits." California EPA Public Health Goal for Trichloroethylene in Drinking Water (July 2009), at 21.

[54] Johnson, PD, *et al.*, Environ Health Perspect 122: A94 (2014): erratum to Johnson, PD, *et al.*, Environ Health Perspect 113:A18 (2005), which is an erratum to Johnson *et al.* (2003).

[55] TCE Developmental Cardiac Toxicity Assessment Update (available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2012-0723-0045).

- It is a screening level assessment which does not meet OMB guidelines implementing the Information Quality Act for a "highly influential scientific assessment" to support TSCA § 6 rulemaking.

- The report of the peer review of the TCE Assessment highlights the foregoing points in the clearest possible terms, but EPA ignored it.[56] In fact, the EPA Assistant Administrator characterized the peer review as supportive.

Following enactment of the Lautenberg Act, it should be clear that a risk evaluation that supports a TSCA § 6 rule must be more robust than the screening level Work Plan Assessment that EPA conducted for TCE. Peer review and public comments identified numerous scientific deficiencies with the draft assessment, including the inappropriate use of default assumptions; ignoring contrary evidence that affects the weight of the scientific evidence; reliance on inapposite exposure data; conclusions inconsistent with the evidence cited; and reliance on a study that is not reproducible. Important shortcomings in both the hazard and exposure assessments were noted. Whatever "best available science" may mean, it cannot include reliance on an unreproducible toxicity study, a cancer risk assessment that does not take into account relevant epidemiological and toxicological studies, or outdated and unrepresentative exposure information.[57] And certainly EPA can no longer afford to ignore the conclusions of the peer review it initiated, as TSCA § 26(h) requires it to consider "the extent of independent verification or peer review of the information."

II. Failure to Comply with SBREFA

The Regulatory Flexibility Act, as amended by the Small Business Regulatory Enforcement Fairness Act (SBREFA), provides:

> "(a) When any rule is promulgated which will have a significant economic impact on a substantial number of small entities, the head of the agency promulgating the rule or the official of the agency with statutory responsibility for the promulgation of the rule shall assure that small entities have been given an opportunity to participate in the rulemaking for the rule through the reasonable use of techniques such as—
>
> (1) the inclusion in an advance notice of proposed rulemaking, if issued, of a statement that the proposed rule may have a significant economic effect on a substantial number of small entities;
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> (2) the publication of general notice of proposed rulemaking in publications likely to be obtained by small entities;
>
> (3) the direct notification of interested small entities;

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[56] https://www.epa.gov/sites/production/files/2015-09/documents/tce_consolidated_peer_review_comments_september_5_2013.pdf.

[57] *See* 162 Cong. Rec. S3522 (June 7, 2016) ("For far too long Federal agencies have manipulated science to fit predetermined political outcomes, hiding information and underlying data, rather than using open and transparent science to justify fair and objective decision making. This Act seeks to change all of that and ensure that EPA uses the best available science, bases scientific decisions on the weight of the scientific evidence rather than one or two individual cherry-picked studies, and forces a much greater level of transparency that forces EPA to show their work to Congress and the American public.)"

(4) the conduct of open conferences or public hearings concerning the rule for small entities including soliciting and receiving comments over computer networks; and

(5) the adoption or modification of agency procedural rules to reduce the cost or complexity of participation in the rulemaking by small entities.

"(b) Prior to publication of an initial regulatory flexibility analysis which a covered agency is required to conduct by this chapter—

(1) a covered agency shall notify the Chief Counsel for Advocacy of the Small Business Administration and provide the Chief Counsel with information on the potential impacts of the proposed rule on small entities and the type of small entities that might be affected;

(2) not later than 15 days after the date of receipt of the materials described in paragraph (1), the Chief Counsel shall identify individuals representative of affected small entities for the purpose of obtaining advice and recommendations from those individuals about the potential impacts of the proposed rule;

(3) the agency shall convene a review panel for such rule consisting wholly of full time Federal employees of the office within the agency responsible for carrying out the proposed rule, the Office of Information and Regulatory Affairs within the Office of Management and Budget, and the Chief Counsel;

(4) the panel shall review any material the agency has prepared in connection with this chapter, including any draft proposed rule, collect advice and recommendations of each individual small entity representative identified by the agency after consultation with the Chief Counsel, on issues related to subsections 603(b), paragraphs (3), (4) and (5) and 603(c);

(5) not later than 60 days after the date a covered agency convenes a review panel pursuant to paragraph (3), the review panel shall report on the comments of the small entity representatives and its findings as to issues related to subsections 603(b), paragraphs (3), (4) and (5) and 603(c), provided that such report shall be made public as part of the rulemaking record; and

(6) where appropriate, the agency shall modify the proposed rule, the initial regulatory flexibility analysis or the decision on whether an initial regulatory flexibility analysis is required."[58]

No Small Business Advisory Review (also referred to as "SBREFA Panel") was held for the proposed rule, however. Instead, EPA determined and certified that the rule would "not, if promulgated, have a significant economic impact on a substantial number of small entities." Where such a certification is made, no initial or final regulatory analysis is required, and thus a SBREFA Panel need not be convened.[59]

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[58] 5 U.S.C. § 609(a), (b).

[59] 5 U.S.C. § 605(b): "Sections 603 and 604 of this title shall not apply to any proposed or final rule if the head of the agency certifies that the rule will not, if promulgated, have a significant economic impact on a substantial number of small entities. If the head of the agency makes a certification under the preceding sentence, the agency

HSIA submits that EPA could not lawfully have certified that the proposed rule banning the use of TCE in spot cleaning lacked SISNOSE. EPA has adopted guidance on making the SISNOSE determination:

> "The lower economic impact threshold is particularly important because it is used to screen out rules that generally will not have a significant economic impact and, therefore, can be presumed not to require an IRFA/FRFA (i.e., if all small entities subject to a rule face economic impacts less than the lower threshold, then the rule may be assigned to the Presumed No SISNOSE Category). For this reason the lower economic impact threshold should be set conservatively, at a level that precludes any reasonable possibility that a rule placed in the Presumed No SISNOSE Category might later be found to impose a "significant economic impact on a substantial number of small entities." The upper threshold defines a level of economic impact that would be unquestionably significant for a small entity. In analyzing previous rules, EPA has often defined the lower threshold as compliance costs of 1% of sales and the higher threshold as compliance costs of 3% of sales as shown in the example in Table 2."[60]

The guidance further states that where the number of small entities subject to the rule and experiencing given economic impact is 1,000 or more, regardless of the percentage these constitute of all the small entities subject to the rule that are experiencing given economic impact, the rule will be presumed ineligible for certification.[61]

Spot cleaning is conducted by dry cleaners, virtually all of which are small businesses. The National Cleaners Association (NCA) estimates that there are some 23,550 retail dry cleaning establishments in the United States, having average sales of $250,797 and average profits of $17,809. Industry suppliers report that 60-90% of retail dry cleaners routinely order TCE for use on the spotting board (14,130 – 21,195 small businesses).

During an EO 12866 meeting on October 3, 2016, NCA provided the foregoing and following information. TCE is one of the most used spotting agents. TCE's effectiveness as a spot remover helps cleaners minimize time spent in stain removal and therefore control labor and operational costs. In most small dry cleaning plants the stain removal technician is the highest paid employee. Depending on the operation, labor represents 25-42% (average 30%) of the dry cleaners' costs. Assuming that only twelve garments a day require five additional minutes of stain removal time, this will add one hour a day to the spotter's labor. Assuming the spotter earns just $35,000 per year, one extra hour per day in a 6-day week, with overtime involved, will result in an extra $7,875 in the spotter's gross wages. It will also result in increased utilities due to six additional hours per week of boiler time and plant operation. It will also result in wasted or slowed production in the pressing department as they wait longer for cleaned

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shall publish such certification in the Federal Register at the time of publication of general notice of proposed rulemaking for the rule or at the time of publication of the final rule, along with a statement providing the factual basis for such certification."

[60] Final Guidance for EPA Rulewriters: Regulatory Flexibility Act as amended by the Small Business Regulatory Enforcement Fairness Act, https://www.epa.gov/sites/production/files/2015-06/documents/guidance-regflexact.pdf, Table 2.

[61] *Id.*

garments, further increasing labor costs. Between labor and utilities, NCA estimated *an increased cost of between 4–5% of gross sales.*[62]

Even the lowest increased cost estimated by NCA (4% of gross sales), at the low end of the range of small dry cleaning entities (14,130), constitutes SISNOSE as defined in EPA's guidance. The economic analysis in the docket acknowledges a much larger universe of dry cleaning that use spot removers (48,602) but concludes, with no factual support, that all of these are expected to experience cost impacts that are less than one percent of their revenues.[63]

Remarkably, neither the preamble to the proposed rule nor the economic analysis contains a detailed "statement providing the factual basis for such certification [of no SISNOSE] required by law." Rather, the latter includes a remarkably abstruse discussion of "market failure" that could be inserted into any analysis to support regulation in the absence of data specific to an industry or small business sector.[64] It is respectfully submitted that this does not meet the requirements of the Regulatory Flexibility Act.

III. Failure to Comply with Notice Requirements of TSCA and Administrative Procedure Act

EPA's TCE Work Plan Assessment is legally deficient in a more fundamental way. The draft Assessment was entitled "Degreaser and Arts/Crafts Uses." It states that "EPA focused the assessment on uses of TCE as a degreaser (i.e., both in small commercial settings and by consumers or hobbyists) and on consumer use of TCE in products used by individuals in the arts and crafts field" (p. 14). Spot cleaning is mentioned only in fn. 8: "there were several spot cleaners for fabrics marketed to consumers, but none contained TCE; lists of ingredients were not available for a few of the spot cleaners." There was no reference at all to spot cleaning in the workplace. Yet, with no explanation, the final TCE Work Plan Assessment is entitled "Degreasing, *Spot Cleaning* and Arts & Crafts Uses" and includes "Commercial use of TCE as a spotting agent at dry cleaning facilities" (p. 26).

The failure to notify dry cleaners that EPA was assessing a key agent upon which they rely clearly violates TSCA § 6(b)(4)(H), which states: "The Administrator shall provide no less than 30 days

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[62] https://www.reginfo.gov/public/do/viewEO12866Meeting?viewRule=true&rin=2070-AK03&meetingId=2352&acronym=2070-EPA/OCSPP

[63] *See* Economic Analysis of Proposed TSCA Section 6 Action on Trichloroethylene in Dry Cleaning Spot Removers and Aerosol Degreasers, at ES-15. The difference in number of establishments is due to EPA's reliance on data from decades ago when dry cleaning was a much larger sector.

[64] It begins:

> "Market failure can justify government regulation; the major types of market failures include the following:
>
> - Negative externalities, common property resources, and public goods;
> - Market power;
> - Inadequate or asymmetric information.
>
> The occurrence of any of these conditions justifies further inquiry into the need for government regulation to reduce inefficiencies in the allocation of society's resources. This section describes why negative externalities and inadequate or asymmetric information are present in the market for dry cleaning spot removers and aerosol degreasing products."

Id. at 2-2.

public notice and an opportunity for comment on a draft risk evaluation prior to publishing a final risk evaluation." That this is an "applicable requirement[] of § 6" for purposes of TSCA § 26(l)(4), which sets forth the requirements for EPA to rely upon risk assessments completed prior to enactment of the Lautenberg Act, should be obvious. In addition, § 553 of the Administrative Procedure Act (APA) requires all federal agencies to provide public notice and an opportunity for comment on all proposed rules.[65] The APA definition of "rule" is broad and encompasses background data upon which the rule is based.

Because there was no notice that EPA was addressing spot cleaning, there was no participation by dry cleaner representatives and no peer review of the spot cleaning assessment. EPA based estimates of workers/bystanders on census data "not adjusted to exclude job categories that likely would not be present at dry cleaning facilities. Thus, EPA's estimate likely overestimates the size of the population exposed."[66] Moreover, EPA relied solely on a 2007 California study, which it recognized may not be representative of US dry cleaning facilities. As dry cleaners had no notice that EPA was assessing spot cleaning in the workplace, they did not have an opportunity to comment on the exposure estimates or the study. Thus, the minimal requirements of administrative procedure have not been met in this rulemaking.

An equally serious notice issue is presented by EPA's acknowledgement that it only evaluated the commercial use of TCE for spot cleaning at dry cleaning facilities in the final Work Plan Assessment in response to a peer reviewer comment. It is therefore obvious that the evaluation of this additional use in the final risk assessment was not itself actually peer reviewed. Similarly, the supplemental analyses conducted by EPA to identify risks for the commercial aerosol degreasing use scenario and for various parameters of exposure scenarios for TCE spot cleaner use in dry cleaning facilities were only done long after completion of the Work Plan Assessment and after passage of the Lautenberg Act. Further, these analyses have not been peer reviewed. As noted above, peer review of these analyses is required by the OMB Final Information Quality Bulletin for Peer Review and TSCA.

IV. EPA's Reliance on Alternatives is Unrealistic

TSCA § 6(c)(2) provides:

> "(C) CONSIDERATION OF ALTERNATIVES.—
>
> "Based on the information published under subparagraph (A), in deciding whether to prohibit or restrict in a manner that substantially prevents a specific condition of use of a chemical substance or mixture, and in setting an appropriate transition period for such action, the Administrator shall consider, to the extent practicable, whether technically and economically feasible alternatives that benefit health or the environment, compared to the use so proposed to be prohibited or restricted, will be reasonably available as a substitute when the proposed prohibition or other restriction takes effect."

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[65] 5 U.S.C. § 553(b), (c): "General notice of proposed rulemaking shall be published in the Federal Register, unless persons subject thereto are named and either personally served or otherwise have actual notice thereof in accordance with law. . . . After notice required by this section, the agency shall give interested persons an opportunity to participate in the rulemaking through submission of written data, views, or arguments with or without opportunity for oral presentation."

[66] TCE Work Plan Assessment, at 116.

The proposal suggests that n-propyl bromide (nPB), perchloroethylene, methylene chloride, and water-based compounds could be used as alternatives to TCE in spot cleaning. Many of these alternatives are ineffective, hence the continued market dominance of the TCE-based products. Moreover, there is serious question whether a number of these alternatives would realistically be available, given the designation of nPB, perchloroethylene, and methylene chloride as priorities for risk evaluation/regulation under TSCA § 6(b)(2)(A).[67]

Query how compounds such as nPB could be considered a "reasonably available" substitute for TCE, much less how EPA could consider making such a finding in light of the fact that substitution on nPB in foam fabrication following reduction of the workplace limit for methylene chloride is regarded as a textbook example of "regrettable substitution." Unlike TCE, which has a long history of safe use in the workplace, the serious health impairments suffered by workers in those facilities have been widely documented. Moreover, an nPB industry representative stated at EPA's February 14, 2017 meeting on scoping documents for the ten priority compounds that nPB is no longer used in dry cleaning at all.

V. Gap Filling Purpose of TSCA

As originally enacted and as updated by the Lautenberg Act, TSCA requires EPA to consult and coordinate with other federal agencies "for the purpose of achieving the maximum enforcement of this Act while imposing the least burdens of duplicative requirements on those subject to the Act and for other purposes."[68] Worker and consumer health and safety fall under the jurisdictions, respectively, of OSHA and the Consumer Product Safety Commission (CPSC). The use of TCE in spot cleaning and aerosol degreasing is already more than adequately regulated under the OSH Act and/or the Federal Hazardous Substances Act. This comprehensive regulatory framework provides adequate protections with respect to the same potential adverse impacts and potential exposure pathways targeted by the proposed rule. Taking steps that may lead to the removal of products from the marketplace because workers or consumers failed to comply with the existing legal requirements is not consistent with TSCA either as initially enacted or as revised.

The basis for EPA's broad assertion of jurisdiction over occupational and consumer uses is unclear. The Lautenberg Act eliminated the requirement in TSCA § 6(a) that EPA protect "against [unreasonable] risk using the least burdensome requirements," but did not materially change the existing framework that requires unreasonable risks to be addressed under statutory authority other than TSCA wherever possible. EPA's longstanding interpretation of this framework is as follows:

> "Under section 9(a)(1) of TSCA, the Administrator is required to submit a report to another Federal agency when two determinations are made. The first determination is that the Administrator has reasonable basis to conclude that a chemical substance or mixture presents or will present an unreasonable risk of injury to health or the environment. The second determination is that the unreasonable risk may be prevented or reduced to a sufficient extent by action taken by another Federal agency under a Federal law not administered by EPA. Section 9(a)(1) provides that where the Administrator makes these two determinations, EPA must provide an opportunity to the other Federal agency to assess the risk described in the report, to interpret its own statutory authorities, and to initiate an action under the Federal laws that it administers.
>
> "Accordingly, section 9(a)(1) requires a report requesting the other agency: (1) To determine if the risk may be prevented or reduced to a sufficient extent by action taken

[67] 81 Fed. Reg. 91927 (Dec. 19, 2016).

[68] TSCA § 9(d).

under its authority, and (2) if so, to issue an order declaring whether or not the activities described in the report present the risk described in the report.

"Under section 9(a)(2), EPA is prohibited from taking any action under section 6 or 7 with respect to the risk reported to another Federal agency pending a response to the report from the ether Federal agency. There would be no similar restriction on EPA for any risks associated with a chemical substance or mixture that is not within the section 9(a)(1) determinations and therefore not part of the report submitted by EPA to the other Federal agency."[69]

It was clear from the outset that TSCA is to be used only when other statutes fail to provide a remedy for unreasonable risks. When TSCA was enacted in 1976, Representative James Broyhill of North Carolina indicated that "it was the intent of the conferees that the Toxic Substance Act not be used, when another Act is sufficient to regulate a particular risk."[70] TSCA § 9(a) is substantively unchanged by the Lautenberg Act. The House Energy and Commerce Committee Report states: "H.R. 2576 reinforces TSCA's original purpose of filling gaps in Federal law that otherwise did not protect against the unreasonable risks presented by chemicals," and further clarifies that "while § 5 makes no amendment to TSCA § 9(a), the Committee believes that the Administrator should respect the experience of, and defer to other agencies that have relevant responsibility such as the Department of Labor in cases involving occupational safety."[71]

Colloquies on the floor of the House of Representatives make this intent clear with specific reference to TCE, most notably the following:

"Mr. SHIMKUS. Mr. Speaker, I yield 2 minutes to the gentlewoman from Tennessee (Mrs. *Blackburn*), the vice chair of the full committee.

Mrs. BLACKBURN. Mr. Speaker, I do rise in support of the amendments to H.R. 2576, and I congratulate Chairman *Shimkus* on the wonderful job he has done. Mr. Speaker, I yield to the gentleman from Illinois (Mr. *Shimkus*) for the purpose of a brief colloquy to clarify one important element of the legislation.

Mr. Chairman, it is my understanding that this bill reemphasizes Congress' intent to avoid duplicative regulation through the TSCA law. It does so by carrying over two important EPA constraints in section 9 of the existing law while adding a new, important provision that would be found as new section, 9(b)(2).

It is my understanding that, as a unified whole, this language, old and new, limits the EPA's ability to promulgate a rule under section 6 of TSCA to restrict or eliminate the use of a chemical when the Agency either already regulates that chemical through a different statute under its own control and that authority sufficiently protects against a risk of injury to human health or the environment, or a different agency already regulates that chemical in a manner that also sufficiently protects against the risk identified by EPA.

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[69] 4,4'-Methylenedianiline; Decision to Report to the Occupational Safety and Health Administration, 50 Fed. Reg. 27674 (July 5, 1985). EPA also has acted under § 9(a) to refer 1,3-butadiene and glycol ethers to OSHA, 50 Fed. Reg. 41393 (Oct. 10, 1985) and 51 Fed. Reg. 18488 (May 20, 1986), respectively, and to refer dioxins in bleached wood pulp and paper products to the Food and Drug Administration, 55 Fed. Reg. 53047 (Dec. 26, 1990).

[70] 122 Cong. Rec. H11344 (Sept. 28, 1976).

[71] H. Rep. No. 114-176 (114th Cong., 1st Sess.) at 28.

Would the chairman please confirm my understanding of section 9?

Mr. SHIMKUS. Will the gentlewoman yield?

Mrs. BLACKBURN. I yield to the gentleman from Illinois.

Mr. SHIMKUS. The gentlewoman is correct in her understanding.

Mrs. BLACKBURN. I thank the chairman. The changes you have worked hard to preserve in this negotiated bill are important. As the EPA's early-stage efforts to regulate methylene chloride and TCE under TSCA statute section 6 illustrate, they are also timely.

EPA simply has to account for why a new regulation for methylene chloride and TCE under TSCA is necessary since its own existing regulatory framework already appropriately addresses risk to human health. New section 9(b)(2) will force the Agency to do just that.

I thank the chairman for his good work."[72]

Indeed, TSCA § 9 was strengthened by the Frank R. Lautenberg Chemical Safety for the 21st Century Act, and it was clear from the outset that TSCA is to be used only when other statutes fail to provide a remedy for unreasonable risks. Representative James Broyhill of North Carolina indicated that "it was the intent of the conferees that the Toxic Substance Act not be used, when another act is sufficient to regulate a particular risk."[73] EPA applied this statutory directive in determining that the risk from 4,4' methylenedianiline (MDA) could be prevented or reduced to a significant extent under the Occupational Safety and Health Act, and referring the matter for action by OSHA.[74] And in an analysis of TSCA § 9, EPA's Acting General Counsel concluded that "Congress expected EPA – particularly where the Occupational Safety and Health Act was concerned – to err on the side of making referrals rather than withholding them."[75]

There is no evidence that EPA has submitted to OSHA "a report which describes such risk and includes in such description a specification of the activity or combination of activities which the Administrator has reason to believe so presents such risk and includes in such description a specification of the activity or combination of activities which the Administrator has reason to believe so presents such risk," as required by TSCA § 9(a)(1). The non-existent report obviously did not "include a detailed statement of the information on which it is based" and was not "published in the Federal Register," as required.

Had the required report been issued, it presumably would have identified how OSHA's authority over the workplace was insufficient to address the risks posed by spot cleaning and aerosol degreasing using TCE. A letter from the Assistant Secretary of Labor for Occupational Safety and Health (undated but apparently issued on April 4, 2016) identifies limits on OSHA's authority to regulate hazardous substances such as TCE, but it does not come close to meeting the requirements of TSCA for EPA action in this case. The April 2016 letter identifies no gap specific to spot cleaning or aerosol degreasing in any particular category of workplace, rather it simply recites how OSHA's authority does not extend to self-employed

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[72] 162 Cong. Rec. H3028 (May 24, 2016).

[73] 122 Cong. Rec. H11344 (Sept. 28, 1976).

[74] 50 Fed. Reg. 27674 (July 5, 1985).

[75] Memorandum to Lee M. Thomas from Gerald H. Yamada, June 7, 1985, p. 2.

workers, military personnel, and consumer uses. But those are limitations that were imposed by Congress and have existed since the Occupational Safety and Health Act was enacted (six years before enactment of TSCA). Those limitations apply to every use of every toxic substance. Congress cannot have meant, in enacting "gap-filling" legislation, to open the door to EPA assuming all authority over the use of hazardous substances in the workplace.

If EPA were to identify a category of exposure deemed to present a risk that is unreasonable, these considerations indicate that referral under § 9(a) would be the appropriate course.[76] It is clear from Section 9(a) that TSCA is to be used only when other statutes fail to provide a remedy for unreasonable risks.

Attachments:

Appendix 1
Appendix 2
Appendix 3
Appendix 4
Appendix 5

[76] As noted above, TSCA § 9(a) provides that if the Administrator has reasonable basis to conclude that an unreasonable risk of injury is presented, and he determines, in his discretion, that the risk may be prevented or sufficiently reduced by action under another federal statute not administered by EPA, then the Administrator shall submit a report to that agency describing the risk. In the report, the Administrator shall request that the agency determine if the risk can be prevented or sufficiently reduced by action under the law administered by that agency; if so, the other agency is to issue an order declaring whether the risk described in the Administrator's report is presented, and is to respond to the Administrator regarding its prevention or reduction. The Administrator may set a time (of not less than 90 days) within which the response is to be made. The other agency must publish its response in the Federal Register. If the other agency decides that the risk described is not presented, or within 90 days of publication in the Federal Register initiates action to protect against the risk, EPA may not take any action under § 6 of TSCA.

HSIA
halogenated solvents industry alliance, inc.

May 29, 2018

Office of the Science Adviser
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket No. EPA-HQ-OA-2018-0259

Dear Sir:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) is pleased to have the opportunity to offer these comments on EPA's proposed rule to strengthen transparency in regulatory science. 83 Fed. Reg. 18768 (April 30, 2018). The intent of this rule is to ensure that EPA uses scientific information in its assessments that is publicly available to allow for independent validation, particularly when the scientific studies are pivotal to regulatory action. HSIA represents producers and users of trichloroethylene (TCE), and HSIA's experience with assessments of that chemical by two EPA program offices has highlighted the need for greater transparency in that process.

In 2011, EPA derived a reference concentration (RfC) of 0.0004 ppm (0.4 ppb or 2 $\mu g/m^3$) and a reference dose (RfD) of 0.0005 mg/kg-day for TCE.[1] EPA's derivation of the RfC/RfD for TCE was based, in part, on Johnson *et al.*, Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat, Environ. Health Perspect. 111: 289-92 (2003). This assessment was subsequently adopted in the TSCA Chemicals Work Plan Assessment for TCE.

As noted in the proposed rule, both transparency and independent validation of key findings of a study (reproducibility) are necessary in EPA's scientific assessments to ensure "that the quality of published information meets the standards of the scientific and technical community." For reasons discussed below, the Johnson *et al.* (2003) study meets neither of these standards and should not be used to develop toxicological values that serve as the basis for regulation.

1. Data records for Johnson *et al.* (2003) are inadequate or non-existent

HSIA's attempts to see the raw data which formed the basis of the Johnson et al. (2003) study report have been unsuccessful. When HSIA requested access to the data used by EPA in its evaluation of the dose-response relationship between TCE exposure and cardiac defects reported in Johnson *et al.* (2003), the Agency provided the spreadsheet, referenced as Johnson (2009) (HERO ID 783484) in the 2011 IRIS Assessment, and indicated that was the entirety of the data evaluated. Examination of that spreadsheet reveals an absence of certain critical information, including most importantly dates for any of the individual treatment/control animals. Acknowledging the documented deficiencies in their paper (and the data provided to EPA), the authors published an erratum aimed at updating the public record regarding methodological issues for Johnson *et al.* (2003). According to Makris *et al.* (2016):

> "some study reporting and methodological details remain unknown, e.g., the precise dates that each individual control animal was on study, maternal body weight/food consumption and clinical observation data, and the detailed results of analytical chemistry

[1] Toxicological Review of Trichloroethylene (CAS No. 79-01-6) in Support of Summary Information on the Integrated Risk Information System (2011).

testing for dose concentration. Additional possible sources of uncertainty identified for these studies include that the research was conducted over a 6-year period, that combined control data were used for comparison to treated groups, and that exposure characterization may be imprecise because tap (rather than distilled) drinking water was used in the Dawson et al. (1993) study and because TCE intake values were derived from water consumption measures of group-housed animals."

HSIA submits that the information contained in the above paragraph alone constitutes a transparency as well as a data quality concern sufficient to preclude Johnson *et al.* (2003) from being used as the basis for regulation. A direct appeal to Dr. Johnson failed to make the data available for public scrutiny. And a Freedom of Information Act request pursuant to the Shelby Amendment was denied by the National Institutes of Health.

The transparency problem with Johnson *et al.* (2003) was pointed out by the peer review of the TSCA Chemicals Work Plan assessment for TCE. An excerpt from the peer review report is reproduced below:

"Unfortunately, Johnson et al (2003) failed to report the source or age of their animals, their husbandry or provide comprehensive historical control data for spontaneous cardiovascular malformations in their colony. The Johnson study with 55 control litters compared to 4 affected litters of 9 treated was apparently conducted over a prolonged period of time (perhaps years); it is possible this was due to the time required to dissect and inspect fresh rodent fetuses by a small academic group. However, rodent background rates for malformations, anomalies and variants show temporal fluctuations (WHO, 1984) and it is not clear whether the changes reported by Johnson et al. (2005) were due to those fluctuations or to other factors. Surveys of spontaneous rates of terata in rats and other laboratory animals are common particularly in pharmaceutical and contract laboratory safety assessments (e.g., Fritz et al., 1978; Grauwiler, 1969; Palmer, 1972; Perraud, 1976). The World Health Organization (1984) advised:

"'Control values should be collected and permanently recorded. They provide qualitative assurance of the nature of spontaneous malformations that occur in control populations. Such records also monitor the ability of the investigator to detect various subtle structural changes that occur in a variety of organ systems.'

"Rates of spontaneous congenital defects in rodents can vary with temperature and housing conditions. For example, depending on the laboratory levocardia and cardiac hypertrophy occur in rats at background rates between 0.8-1.25% (Perraud, 1976). Laboratory conditions can also influence study outcome; for instance, maternal hyperthermia (as a result of ambient elevated temperature or infection) can induce congenital defects (including cardiovascular malformations) in rodents and it acts synergistically with other agents (Aoyama et al., 2002; Edwards, 1986; Zinskin and Morrissey, 2011). Thus while the anatomical observations made by Johnson et al. (2003) may be accurate, in the absence of data on maternal well-being (including body weight gain), study details (including investigator blind investigations), laboratory conditions, positive controls and historical rates of cardiac terata in the colony it is not possible to discern the reason(s) for the unconventional protocol, the odd dose-response and marked differences between the Johnson et al. (2003) results and those of other groups."

"As noted by previous investigators, the rat fetus is 'clearly at risk both to parent TCE and its TCA metabolite' given sufficiently high prenatal TCE exposures that can induce neurobehavioral deficits (Fisher et al, 1999; Taylor et al., 1985), but to focus on cardiac terata limited to studies in one laboratory that have not been reproduced in other (higher dose) studies and apply the BMD01 with additional default toxicodynamic uncertainty factors appears misleading."

HSIA had consistently maintained that the data presented in Johnson *et al.* (2003) and subsequently clarified in the two errata do not allow calculations of the incidence of cardiac malformations per litter that is time-matched to concurrent controls (the standard practice for evaluation of developmental toxicity studies). *Accepting the authors' claim in the 2014 erratum that exposure times cannot be confirmed for substantial amounts of either control or treatment data, it also can be presumed that it is now impossible to reconstruct a calculation of per litter incidence of cardiac malformations that is appropriately matched to concurrent controls.* Thus, the data reported in Johnson *et al.* (2003), even as amended in two subsequent errata, do not allow for data analysis generally accepted as essential to interpreting outcomes of developmental toxicity study findings. The lack of data availability and clarity sufficient to construct key analyses associated with a key study should disqualify the use of that study in important decisions such as RfC/RfD derivations used for regulatory purposes.

2. Johnson *et al.* (2003) is not reproducible

At least two GLP-compliant studies (Carney *et al.* 2006[2]; Fisher *et al.* 2001[3]) conducted under both EPA and Organization for Economic Coordination and Development (OECD) guidelines have been unable to reproduce the effect seen by Johnson *et al.* (2003), despite the participation in one of the studies by Johnson herself. Significant to the proposed transparency rule, Carney *et al.* (2006) was conducted as part of a voluntary testing program between the HSIA and the Agency for Toxic Substances & Disease Registry (ATSDR). All stages of the testing, from development of the protocol to the final report, underwent extensive peer review by scientists from three separate governmental agencies (ASTDR, EPA, and the National Toxicology Program), as well as external experts. In addition, the protocol and study report (which includes the raw data) are available to the public. Carney *et al.* (2006) meets the highest standard of transparency that can be achieved for EPA's assessment needs.

A third guideline study of TCE developmental toxicity is now being sponsored by HSIA, with results expected by September 2018. The study is designed with a focus on cardiac abnormalities and includes toxicokinetic measures to enable comparison with the earlier studies. It is intended to fill the remaining gap for a guideline study by the drinking water route, the same exposure route as Johnson *et al.* (2003). Keeping TCE in the drinking water solutions and achieving acceptable target concentrations of TCE in the drinking water has been challenging because of the high propensity of TCE to volatilize into the air. For this reason, the concentrations of TCE in the drinking water formulations will be sampled prior to transfer into the rat drinking water bottles at multiple times during the study, including time points that bracket the period of fetal heart development. The study will also include a determination on

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[2] Carney, E.W., Thorsrud, B.A., Dugard, P.H., and Zablotny, C.L, Developmental toxicity studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth Defects Res. (Part B) 77: 405-412 (2006).

[3] Fisher, J.W., Channel, S.R., Eggers, J.S., Johnson, P.D., MacMahon, K.L., Goodyear, C.D., Sudberry, G.L., Warren, D.A., Latendresse, J.R., and Graeter, L.J., Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: do they affect fetal rat heart development? Int. J. Toxicol. 20: 257-267 (2001).

how much TCE is lost from the dosing solutions in the water bottles when placed in the animal cages over the course of a 24-hour exposure period. All data will be made publicly available in the study report.

In summary, we support EPA's proposed transparency rule and point to the use of Johnson *et al.* (2003) in EPA's derivation of toxicological values for TCE as an example of why the rule is needed. There has been a great deal of public concern regarding cardiac malformations from exposure to TCE in indoor air as a consequence of EPA's derivation of the IRIS RfC/RfD for TCE using the Johnson *et al.* (2003) study. In 2014, EPA Region 9 issued action levels of 8 $\mu g/m^3$ (commercial and industrial) for an 8-hour workday and 2 $\mu g/m^3$ (residential) for short-term exposures to TCE at Superfund sites under its jurisdiction. The short-term exposure limit of 2 $\mu g/m^3$ is based on the IRIS RfC/RfD for TCE and was intended by Region 9 "to be protective of sensitive and vulnerable populations, especially women in the first trimester of pregnancy, because of the potential for cardiac malformations to the developing fetus." Mitigation measures to achieve this short-term exposure limit include evacuation of residents or workers from buildings. Regions 9's short-term exposure limit is now being adopted by states to protect against the risk of cardiac malformations from TCE exposure in indoor air from contaminated sites, even though the more relevant route of exposure for this regulatory action by federal and state agencies is by inhalation of TCE vapor and not orally from drinking water. The only animal developmental study conducted on TCE by the inhalation route (Carney *et al.* 2006) showed no indication of developmental toxicity, including cardiac malformations.

Respectfully submitted,

Faye Graul / wcn

Faye Graul
Executive Director

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFTEY
AND POLLUTION PREVENTION

RE: Meeting with Halogenated Solvents Industry Alliance (HSIA)

List of Documents

1. Meeting Summary
2. Sign-in Sheet

Meeting Summary

On July 12, 2017, EPA met with HSIA on proposed regulations of trichloroethylene (TCE) under TSCA section 6(a). The meeting was attended by HSIA and representative from Parts Cleaning Technologies (PCT). HSIA requested the meeting to provide a summary of the comments they submitted to EPA. Comments submitted by HSIA are available at EPA-HQ-OPPT-2016-0163-0178 and EPA-HQ-OPPT-2016-0387-0698. Comments submitted by PCT are available at EPA-HQ-OPPT-2016-0387-0687.

MEETING SIGN-IN SHEET

Project: TCE Proposed Rulemaking	**Meeting Date: July 12, 2017**
Who: HSIA meeting with DAA	**Place/Room: EPA**

Name	Organization	Phone	E-Mail
JOEL WOLF	EPA	202-564-0437	wolf.joel@epa.gov
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Nancy Beck			

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFTEY
AND POLLUTION PREVENTION

RE: Meeting with Halogenated Solvents Industry Alliance (HSIA)

List of Documents

1. Meeting Summary

Meeting Summary

On July 20, 2017, EPA met with HSIA on proposed regulations of trichloroethylene (TCE) under TSCA section 6(a). This meeting was a follow-up meeting to the July 12 meeting between EPA and HSIA. HSIA provided additional information on the anticipated schedule for completing the HSIA sponsored study of TCE developmental toxicity. HSIA also offered to coordinate a few site visits to vapor degreasing facilities to demonstrate current practices at those facilities.